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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07J 51/00, A61K 31/565 — A1

(11) International Publication Number: WO 98/00438

(43) International Publication Date: 8 January 1998 (08.01.98)

(21) International Application Number: PCT/GB97/01748

(22) International Filing Date: 26 June 1997 (26.06.97)

(30) Priority Data:
9613722.9 28 June 1996 (28.06.96) GB

(71) Applicant *(for all designated States except US)*: THE UNIVERSITY OF LIVERPOOL [GB/GB]; Senate House, Abercromby Square, Liverpool L69 3BX (GB).

(72) Inventors; and

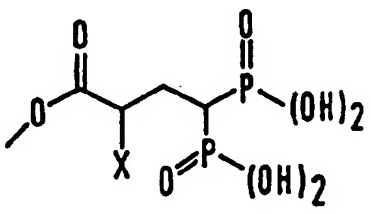
(75) Inventors/Applicants *(for US only)*: GALLAGHER, James, Anthony [GB/GB]; 12 Chetwood Avenue, Crosby L23 2UX (GB). MOORE, Jonathan, Paul, Granville [GB/GB]; 8 Links Close, Churston Ferrers, Brixham, Devon TQ5 0JT (GB). BOWLER, Wayne, Barry [GB/GB]; 52 Town Row, West Derby, Liverpool L12 5HQ (GB). PAGE, Philip, Charles, Bulman [GB/GB]; 203 Forest Road, Loughborough, Leicestershire LE11 3HS (GB).

(74) Agent: SKAILES, Humphrey, John; Frank B Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: STEROID BISPHOSPHONATES



(A)

(57) Abstract

Bisphosphonate derivatives of hydroxy steroids which are bone resorption inhibitors or bone formation stimulators, the derivatives having at least one group A in place of a hydroxy group on the steroid molecule, where A is a group of formula (A) where X is: (i) St-O-CO- where St is the residue of the hydroxy steroid given by removal of an OH group; (ii) R^1-O-CO- where R^1 is an alkyl, alkenyl, cycloalkyl, aralkyl or aryl group, any of which may optionally be substituted; or (iii) a hydrogen atom, and the salts and solvates of these compounds. The steroid is typically 17β-oestradiol, oestrone, testosterone, norethindrone, androsterone, norethandrolone or nandrolone. The derivatives can be used in the treatment of bone disorders such as osteoporosis.

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STEROID BISPHOSPHONATES

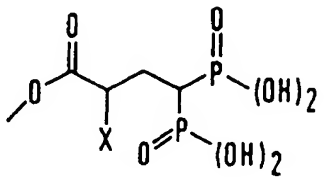
This invention concerns steroid derivatives and in particular bisphosphonate derivatives of hydroxy steroids for use in the prevention or treatment of osteoporosis and related bone disorders.

Hydroxy steroids such as oestradiol and testosterone have been proposed for use in the treatment of osteoporosis, either by inhibition of bone resorption or stimulation of bone formation, and bisphosphonates such as disodium etidronate and clodronate are also known as bone resorption inhibitors. Certain bisphosphonate derivatives of steroids have also recently been proposed for these purposes in EP-A-0496520 and EP-A-0548884. In the compounds of EP-A-0496520 the steroidal group is linked to the bisphosphonate group by a carbamate or carbonate group, and EP-A-0548884 describes steroid bisphosphate ethers.

We have now found a new group of bisphosphonate derivatives of such steroids which are linked by a carboxyl group and, by virtue of the affinity of the bisphosphonate groups for bone, have the potential to target the active steroid selectively on bone and then release the active material in situ by hydrolysis. The compounds of the invention are thus of interest in the prevention or treatment of osteoporosis and other bone disorders such as Paget's disease, bone metastases and malignant hypercalcaemia.

The compounds of the invention are derivatives of hydroxy steroids which are themselves bone resorption inhibitors or bone formation stimulators and thus useful in the prevention or treatment of osteoporosis, the

derivatives having at least one group A in place of a hydroxy group on the steroid molecule, where A is a group of the formula



(A)

where X is:

(i) St-O-CO- where St is the residue of the hydroxy steroid given by removal of an OH group,

(ii) R^1-O-CO- where R^1 is an alkyl, alkenyl, cycloalkyl, aralkyl or aryl group, any of which may optionally be substituted, or

(iii) a hydrogen atom. The invention also includes salts and solvates of these compounds.

The compounds of the invention may thus have the formula St-A where St and A are as defined above. Particular groups of compounds of interest are those of the formulae:

(1) $(St\text{-}O\text{-}CO)_2CHCH_2CH(PO(OH)_2)_2$

(2) $(St\text{-}O\text{-}CO)(R^1\text{-}O\text{-}CO)CHCH_2CH(PO(OH)_2)_2$

(3) $(St\text{-}O\text{-}CO)CH_2CH_2CH(PO(OH)_2)_2$

Where the steroid contains more than one hydroxy group, only one is usually replaced by a group A, but the invention includes derivatives of such compounds in which two or more hydroxy groups are replaced by A groups.

The structural variety of the compounds of the invention allows their hydrolysis properties to be modulated as required. For example, most known steroid-

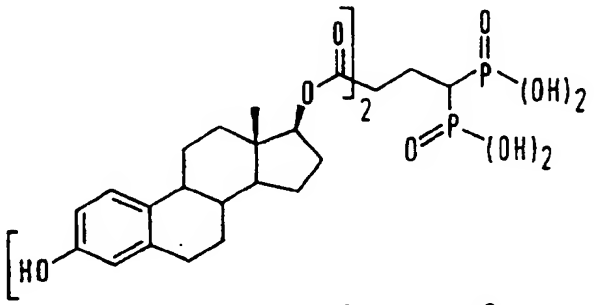
bisphosphonate conjugates, particularly oestradiol-biphosphonates, hydrolyse very rapidly whereas slower hydrolysis and hence slower release of the steroid is often desirable. Compounds of formula (1) above such as the compound (4) below which contains two steroid units are resistant to hydrolysis and thus advantageous when a slower rate of steroid release is required. On the other hand, compounds containing only one steroid unit are less resistant to hydrolysis and thus more suitable when rapid steroid release is required. The compounds of formula (1) also enable two different steroid units to be included in the same molecule, and this allows steroids of different activities to be delivered at the same time.

The parent hydroxy steroid may be an oestrogen, androgen, anabolic steroid, glucocorticoid or progestagen which inhibits bone resorption or stimulates bone formation, such as for example 17β-oestradiol, oestrone, testosterone, norethindrone, androsterone, norethandrolone and nandrolone. These compounds generally have a hydroxy group at the 3- or 17- position or both, and further examples of hydroxy steroids which may be used are listed in EP-A 0496520.

In the group X, R^1 may be a C_{1-6} alkyl (e.g. methyl, ethyl, isopropyl or t-butyl), C_{2-6} alkenyl (e.g. allyl), C_{3-8} cycloalkyl (e.g. cyclopentyl or cyclohexyl), phenyl (C_{1-6})alkyl or a mono- or bicyclic aryl group (e.g. phenyl or naphthyl). The alkyl and alkenyl groups may for example be substituted by one or more halogen atoms (e.g. chlorine) and the cycloalkyl groups by one or more C_{1-4} alkyl groups or halogen atoms (e.g. chlorine). The aryl groups may be substituted by one or more hydroxy groups, as in naphthol.

The compounds of the invention are capable of forming salts with bases and examples of such salts are alkali metal (e.g. sodium) and alkaline earth metal (e.g. calcium) salts. Some compounds of the invention exist in enantiomeric forms and all such forms are included.

Particular compounds of importance have the following formulae:



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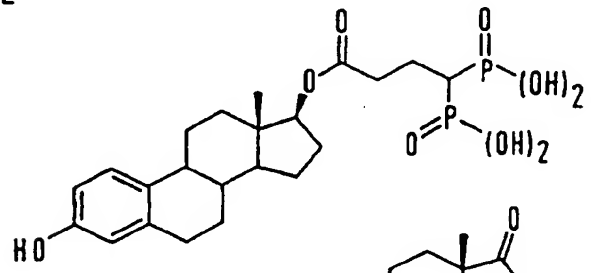

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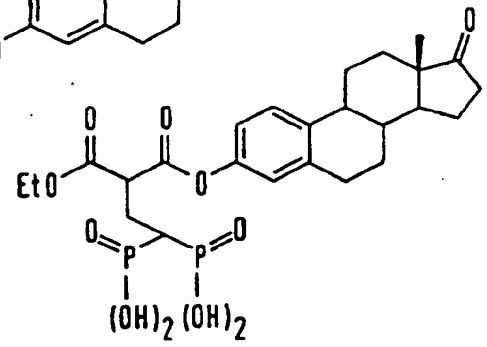


(6)

The compounds of the invention are useful in the prevention or treatment of osteoporosis and the other bone disorders referred to above in man and animals and they may be formulated for these purposes as pharmaceutical compositions together with one or more pharmaceutically acceptable carriers, excipients or

diluents. The active ingredient in these compositions may for example be a compound (4), (5) or (6) shown above.

The pharmaceutical compositions of the invention may be in a form suitable for oral, buccal, parenteral or topical administration.

For oral administration, compositions may be in the form of, for example, tablets, lozenges or capsules containing pharmaceutically acceptable excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents. The tablets may also be coated by known methods. Liquid preparations for oral administration may be in the form of solutions, syrups or suspensions and may contain pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives.

The compositions may also be formulated for use by injection and may be presented in unit dose form, e.g. in ampoules. The compositions for injection may be in the form of suspensions, solutions or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, solubilising and/or dispersing agents.

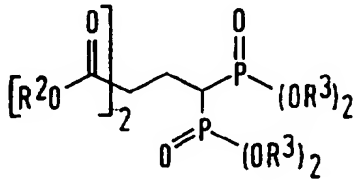
The compositions may also be in a form suitable for topical administration, e.g. transdermal patches, ointments, creams and lotions.

The compounds of the invention may be administered in combination with other pharmaceutically active ingredients.

The total daily dosages of compounds of the invention employed in medicine will suitably be in the range

0.001-10.0 mg/kg bodyweight and these may be given in divided doses, i.e. 1-4 times per day.

Compounds of the invention in which X is a group (i), for example compounds of formula (1) above, may be prepared by transesterification of the carboxylic ester group of a compound of formula (7)



(7)

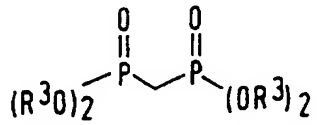
(where R^2 and R^3 are C_{1-6} alkyl groups, e.g. ethyl, and may be the same or different) with the hydroxy steroid (StOH), to give a phosphonate ester (8) of the formula $(St\text{-}O\text{-}CO)_2CHCH_2CH(PO(OR_3)_2)_2$, followed by hydrolysis of the phosphonate ester group to give the desired bisphosphonic acid.

The transesterification of (7) may be effected in the presence of a base catalyst such as DMAP (dimethylaminopyridine), for example in a hydrocarbon solvent at any suitable temperature up to reflux.

When the parent hydroxy steroid contains a further hydroxy group which is to remain in the final product, this should be protected during the transesterification reaction (for example as a benzyl ether) and the protecting group subsequently removed.

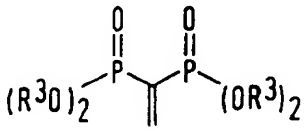
The hydrolysis of the ester (8) may be carried out with a tri (C_{1-6} alkyl) silyl halide such as trimethylsilyl bromide, for example in a halogenated hydrocarbon solvent.

The bisphosphonates (7) may be prepared by first reacting a methylene bisphosphonate (9)



(9)

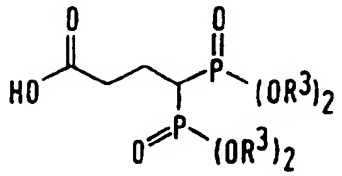
with paraformaldehyde (e.g. in the presence of a base catalyst such as diethylamine) followed by elimination of methanol to give a methylidene compound (10)



(10)

which is then reacted with a dialkylmalonate (in which the alkyl group is R^2 as defined above) in the presence of a base catalyst (e.g. sodium ethoxide).

Compounds in which X is a group (iii), for example compounds of formula (3) above may be prepared by esterification of the hydroxy steroid (StOH) with the acid (11)

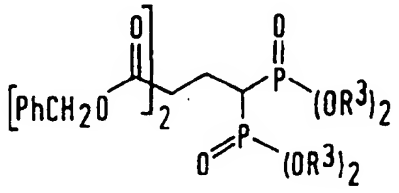


(11)

The reaction may be carried out in the presence of a base and an activating agent such as EDCI (N-(3-ethyldimethylaminopropyl)-N´-ethylcarbodiimide hydrochloride). The phosphonate ester groups may then be removed by hydrolysis as described above to give the required bisphosphonic acid.

Again, when the hydroxy steroid contains a further hydroxy group which is to be retained, it should be protected during the reaction and subsequently removed.

The acids (11) can be prepared from a methylidene compound (10) above by addition of a dibenzyl malonate, in the presence of a non-nucleophilic base catalyst, to give the ester (12)



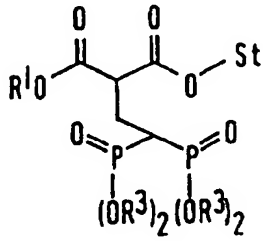
(12)

followed by hydrogenolysis (e.g. over palladium on carbon) and subsequent decarboxylation (e.g. by heating).

Compounds in which X is a group (ii), for example compounds of formula (2) above may be prepared from a malonate (13) of the hydroxy steroid

$$R^1OCO.CH_2.CO.OSt \qquad (13)$$

by reaction with a methylidene compound (10) in the presence of a non-nucleophilic base to give the addition product (14)



(14)

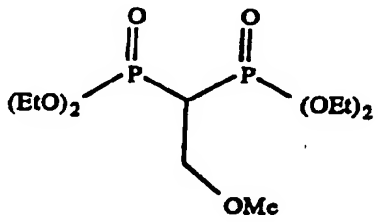
followed by removal of the phosphonate ester group by hydrolysis as described above to give the desired bisphosphonic acid.

The following examples illustrate the invention.

EXAMPLE 1

Synthesis of Tetraethyl ethylidene bisphosphonate (16)

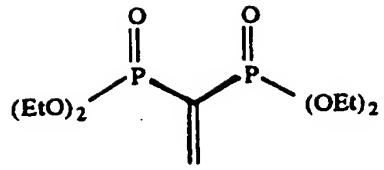
(i)



(15)

Tetraethyl methylene bisphosphonate (47.4 g, 0.165 mol, 1.0equiv.), paraformaldehyde (24.75 g, 0.825 mol, 5.0equiv.), diethylamine (17.1 ml, 12.1 g, 0.165 mol, 1.0equiv.) were added to methanol (470 ml). The reaction mixture was heated at 60 °C until the mixture became a colourless solution (30 minutes), and stirred for a further 15 hours at room temperature. The mixture was concentrated under reduced pressure, and toluene (150 ml) added. The solvent was removed under reduced pressure. The addition of toluene followed by a second concentrating process aided the removal of methanol from the crude viscous intermediate product 15. $\delta_H(CDCl_3)$ 1.29 (12H, t, J = 8, P-$OCH_2\underline{C}H_3$), 2.67 (1H, tt, J_{H-P} = 24, J_{H-H} = 5, $P_2C\underline{H}CH_2OCH_3$), 3.32 (3H, s, -$OCH_3$), 3.86 (2H, td, J_{H-P} = 17, J_{H-H} = 5, $P_2CHC\underline{H}_2OCH_3$), and 4.15 (8H, m, P-$O\underline{C}H_2CH_3$).

(ii)

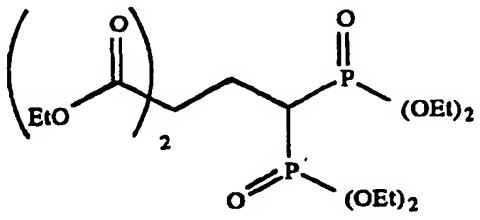


(16)

Toluene-p-sulfonic acid (0.15 g, catalytic) was added to a solution of crude tetraethyl (2-methoxy) ethylidene bisphosphonate 15 in toluene (250 ml). The reaction mixture was heated overnight, under reflux conditions, after this period of time elimination had gone to completion. The reaction mixture was washed with water (3 x 100 ml), and the solvent removed under reduced pressure to yield 16 as an oil (43.16 g, 88% for 2 steps); ν_{max} 3020, 2960, 1485, 1452, 1402, 1270 (b), and 1050 (b); $\delta_H(CDCl_3)$ 1.30 (12H, t, J = 8.0, P-$OCH_2\underline{CH_3}$), 4.0 - 4.2 (8H, m, P-$O\underline{CH_2}CH_3$), and 6.94 (2H, dd, trans J_{P-H} = 40.0, cis J_{P-H} = 36.4, $P_2C=C\underline{H_2}$); $\delta_C(CDCl_3)$ 16.15 (4C, t, J = 3.4, P-$OCH_2\underline{C}H_3$), 63.08 (4C, d, J = 3.4, P-$O\underline{C}H_2CH_3$), 132.58 (1C, t, J = 127, P-$\underline{C}$-P) and 149.11(1C, s, -$P_2C=\underline{C}H_2$); m.s. (CI) *m/z* 301 (M^++H).

EXAMPLE 2

Synthesis of Hexa ethyl-[3,3-bis(oxycarbonyl)]propylidene bis[phosphonate] (17)



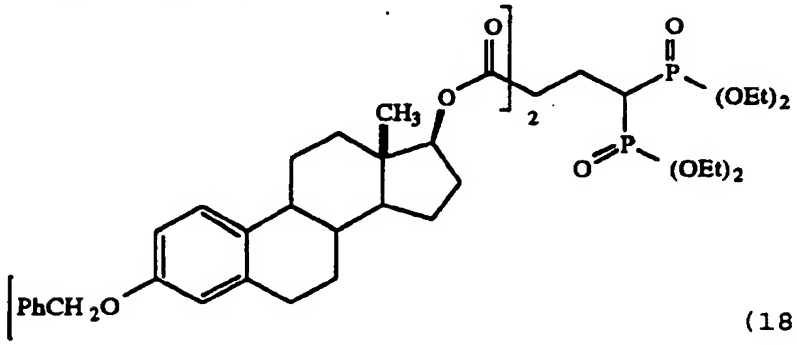
(17)

Sodium (0.23 g, 10 mmol, 0.1 equiv.) was dissolved in ethanol (100ml) and stirred at 0°C under a nitrogen atmosphere. The mixture was allowed to warm to ambient temperature until all the sodium had dissolved. The

sodium ethoxide solution prepared *in situ* was transfered *via* a cannula to a solution of 16 (30.0 g, 100 mmol, 1.0 equiv.) and diethyl malonate (15.20 ml, 16.02 g, 100mmol, 1.0equiv.) in ethanol (50ml). The reaction mixture was stirred under an atmosphere of nitrogen at ambient temperature for 30 minutes. The reaction mixture was washed with aqueous HCl 1M (3 x 100ml) and extracted into CH_2Cl_2 (200ml). The organic fraction was collected and dried with anh. $MgSO_4$, the solvent was removed under reduced pressure final traces of solvent were removed under high vacuum. The desired product 17 was isolated as an oil in excellent yield (43.8g / 95.1%). (Found: C 43.97 H 7.55, $C_{17}H_{34}O_{10}P_2$ requires: C 44.35 H 7.44); ν_{max} 3010, 1749, 1732, 1270 (b), and 1045 (b) cm^{-1}; $\delta_H(CDCl_3)$ 1.28 (6H, t, J = 7.16, $CO_2CH_2\underline{C}H_3$), 1.35 (12H, t, J = 7.12, $PO_2CH_2\underline{C}H_3$), 2.33 - 2.75 (3H, m), 3.97 (1H, t, J = 7.68, $-\underline{C}H(CO_2Et)_2$), and 4.12 - 4.27 (12H, m); $\delta_C(CDCl_3)$ 14.48 (2C, s, $-CO_2CH_2\underline{C}H_3$), 16.71 (4C, d, J_{CP} = $PO_2CH_2\underline{C}H_3$), -25.29 (1C, t, J_{CP} = 5, $-CH\underline{C}H_2CH-$), 34.71 (1C, t, JCP = 132, P-$\underline{C}$-P), 50.51 (1C, t, J_{CP} = 8, $-CH_2\underline{C}H(CO_2Et)_2$, 61.97 (2C, s, $-CO_2\underline{C}H_2CH_3$), 63.22 (4C, t, J_{CP} = , $PO_2\underline{C}H_2CH_3$), and 169.31 (2C, s, $-\underline{C}O_2Et$); δ_P $CDCl_3$)22.33; *m/z* (CI) 461 (M^++H).

EXAMPLE 3

Synthesis of Tetraethyl {3,3-bis-[3-benzyloxy-estra-1,3,5-triene-17β-yloxycarbonyl]propylidene} bis[phosphonate] (18)

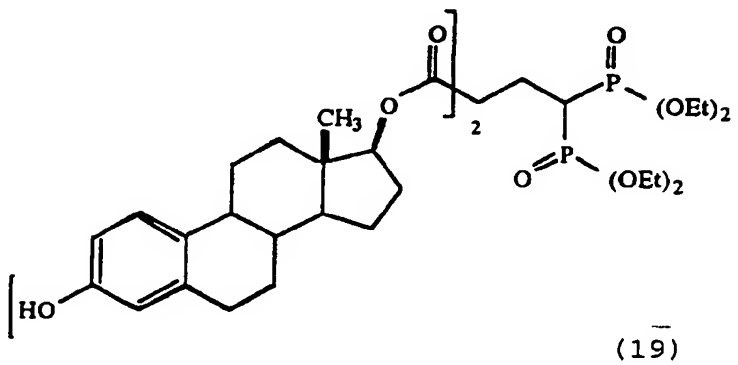


(18)

4-(*N*,*N*-dimethylamino)pyridine (0.013 g, 0.11 mmol, 0.1 equiv.) and 3-benzyl-17β-oestradiol (0.861 g, 2.39 mmol, 2.2 equiv.) were added to a solution of 17 (0.50 g, 1.09 mmol, 1.0 equiv.) in toluene (10 ml). The reaction mixture was heated under reflux for 11 days under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the crude product absorbed onto silica gel. The product was purified by silica gel flash column chromatography, the eluent used was 1-3% methanol in CH_2Cl_2, the desired product was obtained as a viscous oil (0.80 g, 67%); ν_{max} 3017, 2936, 1724, 1605, 1498, 1203 (b), and 929; δ_H ($CDCl_3$) 0.84 (3H, s, 18'-CH_3), 0.88 (3H, s, 18'-CH_3), 1.23 - 1.97 (21H, m), 1.35 (12H, t, J = 7), 2.15 - 2.36 (13H, m), 4.72 - 4.81 (2H, m, 17'H), 5.05 (4H, s, -OC$\underline{H}_2$Ph), 6.74 (2H, s, 4'H), 6.80 (d, 2H, J = 9, 2'H), 7.23 (d, 2H, J = 9, 1'H), and 7.30 - 7.47 (m, 10H); δ_C ($CDCl_3$) 13.09, 13.20, 17.43, 17.51, 24.35, 26.19, 27.24, 28.29, 28.53, 30.82, 35.51 (t, J_{CP} = 132, P$\underline{C}$P), 37.95, 44.15, 44.31, 44.84, 50.80, 51.38 (t, J_{CP} = 7.3, -CH$\underline{C}H_2$CH($CO_2R)_2$), 63.83 (t, J_{CP} = 6.9, -$CH_2\underline{C}$H($CO_2R)_2$), 71.00, 85.02 (d, J_{CP} = 10.4, $PO_2\underline{C}H_2CH_3$), 113.39, 115.92, 127.42, 128.49, 128.89, 129.59, 133.73, 138.39, 138.95, 157.84, and 169.96 (d, J_{CP} = 3.5, -CH($\underline{C}O_2R)_2$); δ_P ($CDCl_3$) 20.4; *m/z* (+ve ion FAB) 1094 (M^++H, 100).

EXAMPLE 4

Synthesis of Tetraethyl {3,3-bis[estra-1,3,5-triene-3-hydroxy-17β-yloxycarbonyl]propylidene} bis[phosphonate] (19)



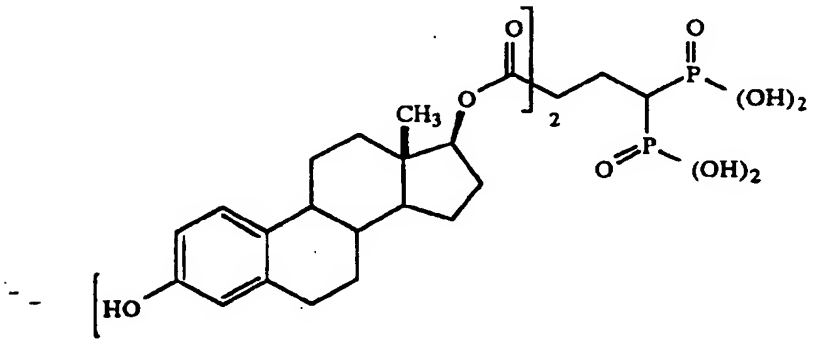
(19)

To a solution containing 18 (692 mg, 0.633 mmol, 1.0 equiv.) in teahydrofuran/methanol 1:1 (10 ml) was added 10% Pd/C (140 mg). The reaction mixture was shaken under an atmosphere of hydrogen (1 bar) for 6 hours. The reaction mixture was filtered, taken up into CH_2Cl_2 and washed with brine. The organic layer was collected and dried with anh. $MgSO_4$ and the solvent removed under reduced pressure. The product was purified further by silica gel flash column chromatography, eluted with 3 - 5% methanol in CH_2Cl_2. The solvent was once again removed and the product was produced as a foam under high vacuum (557mg, 96.4%); (Found: C, 64.68; H, 7.76. $C_{49}H_{70}O_{12}P_2$ requires: C, 64.46; H, 7.73); δ_H ($CDCl_3$) 0.775 (3H, s, 18'-CH_3), 0.781 (3H, s, 18'-CH_3), 1.15 - 1.87 (21H, m), 1.34 (12H, t, J = 6.8, P-$OCH_2\underline{CH}_3$), 2.09 - 2.33 (6H, m), 2.49 (2H,heptet, J = 7.6, $P_2CHC\underline{H}_2CH(CO_2R)_2$), 2.66 (1H, tt, J_{P-H} = 24, J_{H-H} = 7.2 $P_2C\underline{H}CH_2CH(CO_2R)_2$), 2.81 (4H, m), 4.05 (1H, t, J = 7.6, $P_2CHCH_2C\underline{H}(CO_2R)_2$), 4.16 - 4.24 (8H, m, P-$OC\underline{H}_2CH_3$) 4.71 (2H, q, 9.2, 17'H), 6.58 (2H, s, 4'H), 6.66 (2H, d, J = 8, 2'H), and 7.08 (2H, d, J = 8.8, 1'H); δ_C ($CDCl_3$) 11.93 (1C, 18'C), 12.03 (1C, 18'C), 16.29 (4C, d, J = 5, P-$OCH_2\underline{C}H_3$), 23.22 (2C), 24.95 (1C, b -$P_2CH\underline{C}H_2CH$-), 26.16 (2C), 27.18 (1C), 27.37 (1C), 29.53 (2C), 34.17 (1C, t, J = 134, P-$\underline{C}$-P), 36.81 (2C), 38.56

(2C), 42.98 (2C), 43.17 (1C), 43.68 (1C), 49.64 (2C), 50.23 (1C, t, J = 9, $P_2CHCH_2\underline{C}H(CO_2R)_2$) 63.06 (4C, t, J = 7, P-O$\underline{C}H_2CH_3$), 83.95 (1C, 17'C), 84.09 (1C, 17'C), 112.77 (2C), 115.31 (2C), 126.22 (2C), 131.48 (2C), 131.53 (2C), 137.79 (2C), 154.23 (2C), and 168.84 (2C, $-CO_2R$); δ_P ($CDCl_3$) 20.7(s); *m/z* (+ve ion FAB) 913 (M^++H, 76), 159 (100).

EXAMPLE 5

Synthesis of 3,3-Bis-(estra-1,3,5-trien-3-hydroxy-17β-yloxycarbonyl) propylidene bis(phosphonic acid) (20)



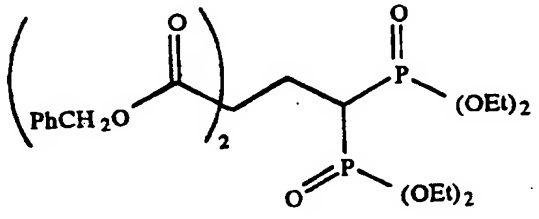
(20)

To a solution of 19 (250 mg, 0.275 mmol, 1.0 equiv.) in CCl_4 / $CHCl_3$ 1:1 (3 ml) was added trimethylsilyl bromide (1.24 ml, 1.47 g, 9.62 mmol, 35 equiv.) and the mixture stirred for 24 hours under a nitrogen atmosphere. Water (5 ml) was added and an off white solid formed. The precipitate was filtered and washed with cold water and CH_2Cl_2. The product was dried under high vacuum and obtained as an off white powder (206 mg, 94%) which decomposes at 180 °C; δ_H (CD_3OD) 0.85 (3H, s, 18'-CH_3), 0.86 (3H, s, 18'-CH_3), 1.20 - 2.05 (21H, m), 2.10 - 2.30 (5H, m), 2.38 - 2.50 (3H, m), 2.70 - 2.81 (4H, m), 4.08 (1H, t, J = 7, $-CH_2\underline{C}H(CO_2H)_2$), 4.72 (2H, t, J = 8, 17'H), 6.47 (2H, d, J = 2, 4'H), 6.53 (2H, dd, J = 9, J = 2, 2'H), and 7.05 (2H, d, J = 9, 1'H); δC (CD_3OD) 12.64 (1C, 18'C), 12.71 (1C, 18'C), 24.22 (2C), 26.37 (1C, b,

-$P_2CH\underline{C}H_2CH$-), 27.44 (2C), 28.45 (2C), 28.52 (2C), 30.63 (2C), 36.79 (1C, t, J = 127, P-$\underline{C}$-P), 38.16 (2C,b), 40.18 (2C), 44.28 (1C, 13'C), 44.40 (1C, 13'C), 45.10 (2C), 50.94 (2C), 52.04 (1C, b, -$\underline{C}H(CO_2R)_2$), 85.26 (1C, 17'C), 85.34 (1C, 17'C), 113.79 (2C), 116.08 (2C), 127.21 (2C), 132.36 (2C), 138.73 (2C), 155.94 (2C, 3'C), and 170.49 (2C, -CO_2R); δ_P (CD_3OD) 22.6; *m/z* (-ve ion FAB) 799 (M^--H, 100).

EXAMPLE 6

Synthesis of Tetraethyl [3,3 bis(benzyloxycarbonyl)]propylidene bis[phosphonate] (21)



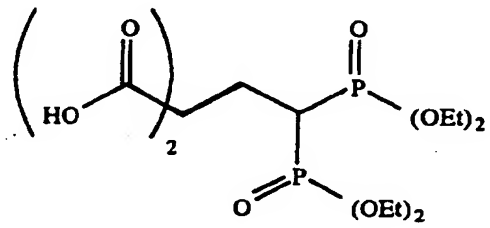
(21)

Tetraethyl ethylidene bisphosphonate 16 (1.00 g, 3.33 mmol, 1.0 equiv.), and dibenzyl malonate (0.83 ml, 0.946 g, 3.33 mmol, 1.0 equiv.) were dissolved in tetrahydrofuran (15 ml). Lithium bis(trimethylsilyl) amide solution in tetrahydrofuran (1M), (0.33 ml, 0.33 mmol, 0.1 equiv.), was added to the reaction mixture and stirred for one hour at room temperature. Saturated aqueous ammonium chloride (50 ml) was added to the reaction mixture and the product extracted into CH_2Cl_2 (100ml). The organic layer was collected and dried with anh. $MgSO_4$, the solvent was removed under reduced pressure. The crude product was absorbed onto silica gel and purified by silica gel flash column chromatography, eluted with 2-3% methanol/ CH_2Cl_2. The product was isolated as a colourless oil (1.12 g, 58% yield); δ_H($CDCl_3$) 1.30 (6H, t, J = 7.1, -$OCH_2C\underline{H}_3$), 1.31 (6H, t, J = 7.1, -$OCH_2C\underline{H}_3$), 2.37 - 2.74 (3H, m), 4.07 - 4.24 (9H, m), 5.14 (4H, s, -$OC\underline{H}_2Ph$), and 7.24 - 7.35 (10H, m);

$\delta_C(CDCl_3)$ 16.10 (2C, $-OCH_2\underline{C}H_3$), 16.24 (2C, $-O\underline{C}H_2CH_3$), 24.81 (1C, m, $-\underline{C}H_2CHP_2$) 34.11 (1C, t, J_{C-P} = 132.1, P-C-P), 49.93 (1C, t, J_{C-P} = 7.8, $-C(O)\underline{C}HRC(O)$), 62.66 (4C, m, $-O\underline{C}H_2CH_3$), 67.11 (2C, $-O\underline{C}H_2Ph$), 128.03 (4C, ortho C), 128.22 (2C, para C), 128.40 (4C, meta C), 135.12 (2C, 1' on Ph) and 168.41 (2C, $-O\underline{C}(O)CH$); $\delta_P(CDCl_3)$ 32.19; *m/z* (+ve ion FAB) (M^++H) 585 (36), 369 (7), and 91 (100); HRMS (M^++H) (Found: 585.20184 $C_{27}H_{39}P_2O_{10}$ requires: 585.20185).

EXAMPLE 7

Synthesis of Tetraethyl 3,3bis(phosphono)-propylidene bis(carboxylic acid) (22)



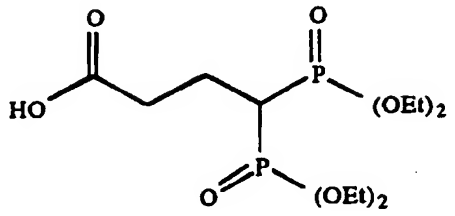
(22)

21 (0.698 g, 1.19 mmol), was dissolved in tetrahydrofuran (10 ml), and palladium activated charcoal (0.10 g, cat.) added. The reaction mixture was stirred under an atmosphere of hydrogen, overnight, at room temperature. The reaction mixture was filtered and washed with saturated aqueous ammonium chloride (50 ml). The product was extracted into CH_2Cl_2 and dried with anh. $MgSO_4$, the solvent was removed under reduced pressure, and the product dried under high vacuum as a white solid, (0.42 g, 88% yield); δ_H(MeOD) 1.35 (12H, t, J = 6.6, $-P-O-CH_2C\underline{H}_3$), 1.74 (2H, heptet, J = 7.7, $P_2CHC\underline{H}_2CH-$), 2.08 (1H, tt, J_{P-H} = 23.1, J = 6.6, $P-C\underline{H}RP$), 3.18 (1H, t, J = 6.6, $-CH_2C\underline{H}(CO_2H)2$), 3.48 - 3.63 (8H, m, $P-O-C\underline{H}_2CH_3$); δC(MeOD) 16.55 (2C, $P-O-CH_2\underline{C}H_3$), 16.68 (2C, $P-O-CH_2\underline{C}H_3$), 25.95 (1C, t, J_{P-C} = 4.0, $P_2CH\underline{C}H_2CH-$), 35.01 (1C, t, J_{P-C} = 133.4, $P-\underline{C}HRP$), 51.10 (1C, m, $-\underline{C}H(CO_2H)_2$), 64.45 (4C, dd, J = 9.4, 6.7, $P-O-\underline{C}H_2CH_3$), 171.84 (2C, $-\underline{C}O_2H$); δ_P(MeOD)

22.8; *m/z* (+ve ion FAB) (M'+D) 406 (100), and (M'+H) 405 (90)

EXAMPLE 8

Synthesis of Tetraethyl 4,4-bis(phosphono)-butanoic acid (23)

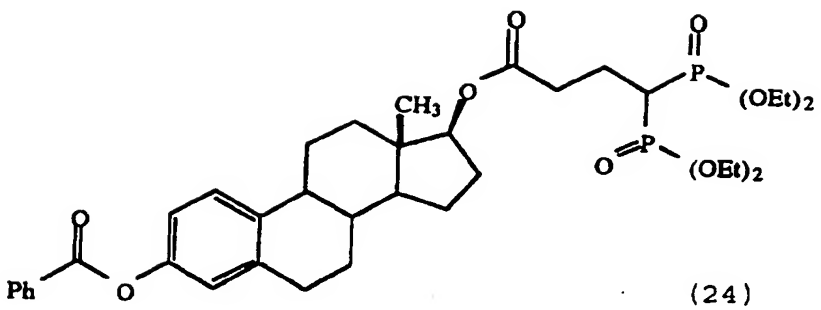


(23)

22 (0.200 g, 0.495 mmol), was heated to 130 °C for 3 hours, under a steady stream of nitrogen. The product was obtained as a colourless oil (0.174 g, 99%); δ_H(MeOD) 1.35 (12H, t, J = 7.7, $-OCH_2C\underline{H}_3$), 2.06 - 2.25 (2H, m, $P_2CHC\underline{H}_2CH_2-$), 2.63 - 2.69 (1H, m, $-CD\underline{H}CO_2H$), 2.81 (1H, tt, J_{P-H} = 24.2, J = 6.6, $-PC\underline{H}P-$), 4.11 - 4.25 (8H, m, P-O-$C\underline{H}_2CH_3$); δ_C (MeOD) 16.57 (2C, P-O-$CH_2\underline{C}H_3$), 16.71 (2C, P-O-$CH_2\underline{C}H_3$), 21.82 - 22.10 (1C, m, $P_2CH\underline{C}H_2CH_2-$), 32.53 - 33.07 (1C, m $P_2CHCH_2\underline{C}H_2CO_2H$), 35.87 (1C, t, J = 133.4, P-$\underline{C}$HR-P), 64.07 - 64.36 (4C, m, P-O-$\underline{C}H_2CH_3$), and 175.85 (1C, $-CO_2H$); δ_P(MeOD) 24.95; *m/z* (-ve ion FAB) 361 (100) (M^--H, for di-deuterated product); HRMS (+ve ion FAB) (Found: 363.12997 $C_{12}H_{25}D_2O_8P_2$ requires: 363.13067).

EXAMPLE 9

Synthesis of Tetraethyl {3-[3-benzoyloxy)estra-1,3,5-trien-17β-yloxycarbonyl] propylidene} bis[phosphonate] (24)



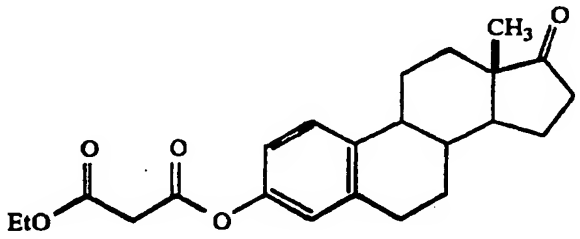
(24)

23 (0.071 g, 0.20 mmol, 1.0 equiv.), 3-O-benzoyl-17β-oestradiol (0.089 g, 0.24 mmol, 1.2 equiv.), and 4-(*N*,*N*-dimethylamino)pyridine (0.005 g, 0.04 mmol, 0.2 equiv.), were dissolved in CH_2Cl_2 (5ml), and stirred at 0 °C under an atmosphere of nitrogen. EDCI (0.0455 g, 0.24 mmol, 1.2 equiv.), was added to the reaction mixture, and allowed to warm slowly to room temperature whilst stirring overnight. The reaction mixture was washed with water (30 ml), and the product extracted into CH_2Cl_2. The organic layer was collected, dried with anh. $MgSO_4$, and the solvent removed under reduced pressure. The crude product was absorbed onto silica gel and purified by silica gel flash column chromatography, 1-3% methanol/ CH_2Cl_2 were used as eluents. The product dried under high vacuum and was isolated as colourless oil (0.048 g, 33%); ν_{max} 3053, 2983, 1729, 1601, 1243, and 1025; $\delta_H(CDCl_3)$ 0.84 (3H, s, 18'-CH_3), 1.25 - 1.93 (11H, m), 1.35 (12H, t, J = 7.2, P-OCH_2CH_3), 1.12 - 2.74 (7H, m), 2.87 - 2.92 (2H, m), 4.12 - 4.28 (8H, m, P-OCH_2CH_3), 4.70 (1H, dd, J = 8.8, 7.1, 17'H), 6.92 - 7.00 (2H, m), 7.33 (1H, d, J = 8.2, 1'H), 7.46 - 7.67 (3H, m), and 8.20 (2H, dt, J = 8.3, 1.6, ortho H's on Ph); $\delta_C(CDCl_3)$ 12.06 (1C, 18'-CH_3), 16.32 (2C, P-OCH_2CH_3), 16.43 (2C, P-OCH_2CH_3), 21.04 (1C, m, $P_2CHCH_2CH_2$-), 23.25 (1C), 26.03 (1C), 27.00 (1C), 27.59 (1C), 29.50 (1C), 35.68 (1C, t, J = 132.1, P_2-CHR), 36.86 (1C), 38.18 (1C), 38.35 (1C), 42.87 (1C), 43.98 (1C), 49.80 (1C), 62.61 (4C, t, J = 6.7, P-OCH_2CH_3), 82.74 (1C, 17'C), 118.67 (1C), 121.58

(1C), 126.43 (1C), 128.49 (2C), 129.70 (1C), 130.10 (2C), 133.45 (1C), 137.84 (1C), 138.19 (1C), 148.68 (1C), and 172.72 (2C); $\delta_P(CDCl_3)$ 23.2; *m/z* (+ve ion FAB) 721 (M^++H, for product containing 2D), 720 (M^++H, for product containing 1D), and 719 (M^++H). The benzyl and ethyl groups can be removed by the methods of Examples 4 and 5.

EXAMPLE 10

Synthesis of Ethyl 17-oxoestra-1,3,5,-trien-3-yl proprionate (25)



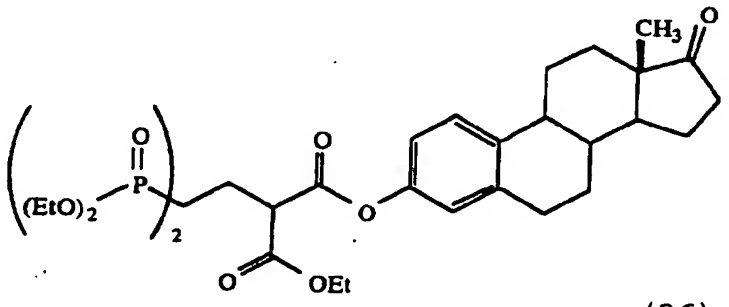
(25)

Oestrone (0.54 g, 2.0 mmol, 1.0 equiv.), triethylamine (0.56 ml, 0.405 g, 4.0 mmol, 2.0 equiv.), were dissolved in tetrahydrofuran (15 ml) and stirred at 0 °C under an atmosphere of nitrogen. Ethyl malonyl chloride (0.76 ml, 0.903 g, 6.0 mmol, 3.0 equiv.) was added slowly to the reaction mixture, which was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with water (2 x 50 ml), and the product extracted into CH_2Cl_2, and dried with anh. $MgSO_4$. The solvent was removed under reduced pressure, the crude product absorbed onto silica gel and purified by silica gel flash column chromatography, eluted with 0.5% methanol/CH_2Cl_2. The product was isolated as a colourless oil (0.144 g,19% yield); $\delta_H(CDCl_3)$ 0.90 (3H, s, 18'-CH_3), 1.32 (3H, t, J = 7.1, -OCH_2CH_3), 1.36 - 1.75 (6H, m), 1.88 - 2.59 (7H, m), 2.91 (2H, dd, J = 8.3, 3.8), 3.59 (2H, s, malonate H), 4.26 (2H, q, 7.1, -OCH_2CH_3), 6.86 - 6.91 (2H, m), and 7.29 (1H, d, J = 8.2, 1'H); $\delta_C(CDCl_3)$

13.65, 13.95, 21.41, 25.60, 26.13, 29.21, 31.39, 35.68, 37.83, 41.47, 43.98, 47.75, 50.26, 61.58, 118.35, 121.18, 126.30, 137.65, 138.00, 148.22 (3'C), 165.25 (-CO_2Et), 166.09 (-CO_2Ph), and 214.04 (17'C); *m/z* (+ve ion FAB) 385 (38) (M^++H), 115 (100).

EXAMPLE 11

Synthesis of Tetraethyl [4-ethoxy-4-oxo-3-(17-oxoestra-1,3,5-trienyloxycarbonyl)-butylidene] bis[phosphonate] (26)



(26)

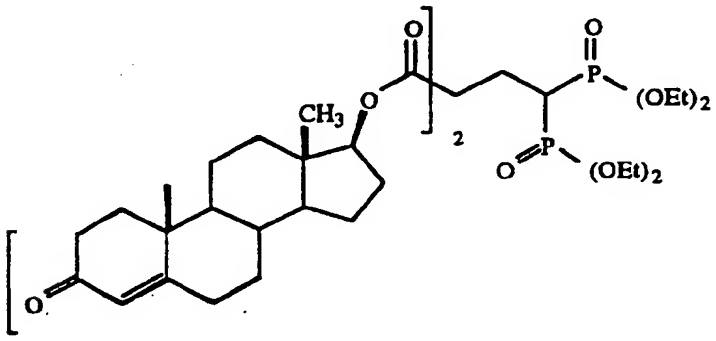
25 (0.112 g, 0.291 mmol, 1.0 equiv.), and 16 (0.087 g, 0.291 mmol, 1.0 equiv.), were dissolved in tetrahydrofuran and stirred at room temperature under an atmosphere of nitrogen. A solution of lithium bis(trimethylsilyl)amide (1M) in tetrahydrofuran (0.03 ml, 0.03 mmol, 0.1 equiv.) was added to the reaction mixture and stirred for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride, and the product extracted into CH_2Cl_2. The organic layer was collected and dried with anh. $MgSO_4$. The solvent was removed under reduced pressure and the crude product adsorbed onto silica gel. The product was purified by silica gel flash column chromatography, 0.5 - 3% methanol/CH_2Cl_2 as eluent. The product was isolated and dried under high vacuum to give a colourless oil (0.060 g, 30%); $\delta_H(CDCl_3)$ 0.91 (3H, s, 18'-CH_3), 1.27 - 1.72 (8H, m), 1.37 (12H, t, J = 7.2, P-O-CH_2CH_3), 1.90 - 2.95 (13H, m), 4.13 - 4.33 (11H, m), 6.82 - 6.90 (2H, m), and

7.30 (1H, d, J = 8.8, 1'H); $\delta_C(CDCl_3)$ 13.76 (1C, 18'C), 14.06 (1C, $-CO_2CH_2\underline{C}H_3$), 16.24 (2C, $-PO_2CH_2\underline{C}H_3$), 16.35 (2C, $-PO_2CH_2\underline{C}H_3$), 21.53 (1C, $P_2CH\underline{C}H_2CH-$), 24.96 (1C, m), 25.70 (1C), 26.24 (1C), 29.32 (1C), 31.50 (1C), 34.28 (1C, t, J = 132.1, P-C-P), 35.76 (1C), 37.97 (1C), 44.11 (1C), 17.86 (1C), 49.93 - 50.23 (1C, m, $-C(O)\underline{C}HRC(O)-$), 50.42 (1C), 61.77 (1C, $-CO_2\underline{C}H_2CH_3$), 62.66 - 62.98 (4C, m, P-O-$\underline{C}H_2CH_3$), 118.35 (1C), 121.18 (1C), 126.36 (1C), 137.70 (1C), 138.08 (1C), 148.38 (1C), 167.73 (1C),168.54 (1C), and 214.15; $\delta_P(CDCl_3)$ 22.34, and 22.44; *m/z* (+ve ion FAB) 685 (57) (M^++H), 239 (100); HRMS (Found: 685.29124 $C_{33}H_{50}O_{11}P_2$ requires: 685.29066).

(26) may be converted to the corresponding bisphosphonic acid by the method of Example 5.

EXAMPLE 12

Synthesis of Tetraethyl {3,3-bis[androst-4-en-3-one-17β-yloxycarbonyl]propylidene} bis[phosphonate] (27)



(27)

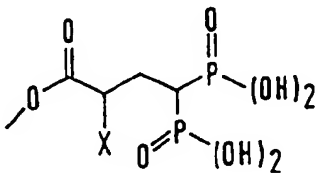
Testosterone (0.500 g, 1.73 mmol, 2.2 equiv.), 17 (0.363 g, 0.788 mmol, 1.0 equiv.), and 4-(*N,N*-dimethylamino)pyridine, were dissolved in toluene (7 ml) and heated under reflux, under an atmosphere of nitrogen. After 10 days reflux, more testosterone (0.250 g, 0.86 mmol, 1.1 equiv.) was added to the reaction mixture, and heated under reflux conditions for another 6 days. The reaction was stopped and washed with

saturated aqueous ammonium chloride. The product was extracted into CH_2Cl_2, and dried with anh. $MgSO_4$. The solvent was removed under reduced pressure, and the crude product absorbed onto silica gel. The product was purified by silica gel flash column chromatography, 3% methanol/CH_2Cl_2 was used as the eluent. The product was isolated as a foam under a high vacuum (0.61 g, 82% based on 3); δ_H ($CDCl_3$), 0.76 (3H, s, 18'-CH_3), 0.78 (3H, s, 18'-CH_3), 0.80 - 1.80 (20H, m), 1.12 (6H, s, 19'-CH_3), 1.28 (12H, t, J = 7.2), 1.94 -1.98 (2H, m), 2.05 -2.57 (13H, m), 3.94 (1H, t, J = 7.6, malonate H), 4.58 (2H, q, J = 8, 17'H), and 5.66 (2H, s, 4'H); δ_C ($CDCl_3$), 11.91 (1C), 12.02 (1C), 16.31 (2C), 16.42 (2C), 17.39 (2C), 20.49 (2C), 23.45 (2C), 24.82 - 25.02 (1C, m), 27.31 (2C), 31.43 (2C), 32.67 (2C), 33.88 (2C), 34.34 (1C, t, J = 133.4), 35.34 (2C), 35.69 (2C), 36.53 (2C), 38.57 (2C), 42.56 - 42.72 (2C, m), 50.17 (2C), 53.61 (2C), 61.51 (1C), 62.61 - 62.92 (4C, m), 83.50 (1C), 83.64 (1C), 123.97 (2C), 168.80 (1C), 168.88 (1C), 170.77 (2C), and 199.37 (2C); δ_P ($CDCl_3$), 22.98; *m/z* (+ve ion FAB) (M^++H) 946 (14), 703 (87), and 461 (100).

(27) may be converted to the corresponding bisphosphonic acid by the method of Example 5.

CLAIMS

1. Bisphosphonate derivatives of hydroxy steroids which are bone resorption inhibitors or bone formation stimulators, the derivatives having at least one group A in place of a hydroxy group on the steroid molecule, where A is a group of the formula



(A)

where X is:

(i) St-O-CO- where St is the residue of the hydroxy steroid given by removal of an OH group;

(ii) R^1-O-CO- where R^1 is an alkyl, alkenyl, cycloalkyl, aralkyl or aryl group, any of which may optionally be substituted; or

(iii) a hydrogen atom,

and the salts and solvates of these compounds.

2. Compounds according to claim 1 of the formula (1)

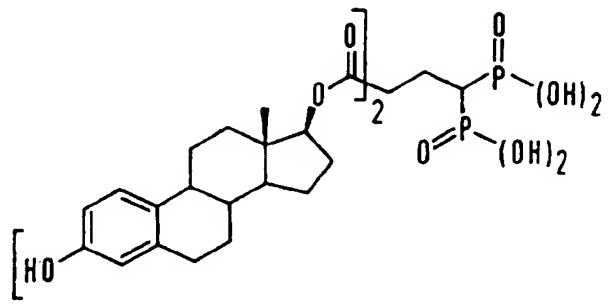
$$(St\text{-}O\text{-}CO)_2CHCH_2CH(PO(OH)_2)_2$$

3. Compounds according to claim 1 or claim 2 wherein the steroid is an oestrogen, androgen, anabolic steroid, glucocorticoid or progestagen.

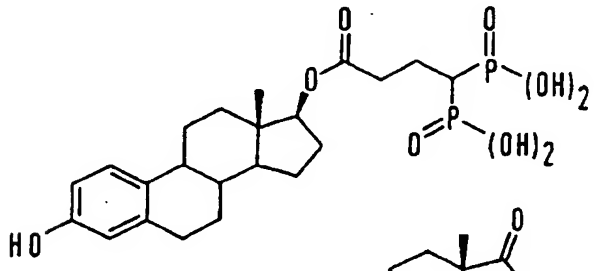
4. Compounds according to claim 1 or claim 2 wherein the steroid is 17β-oestradiol, oestrone, testosterone, norethindrone, androsterone, norethandrolone or

nandrolone.

5. A compound according to claim 1, said compound being:

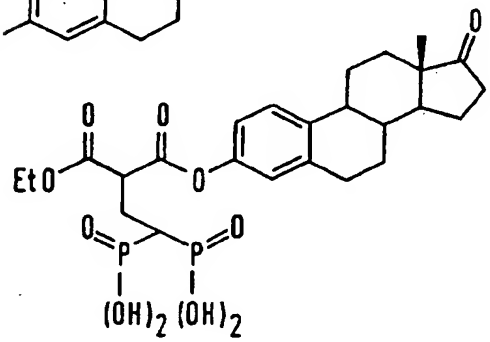


(4)



(5)

or

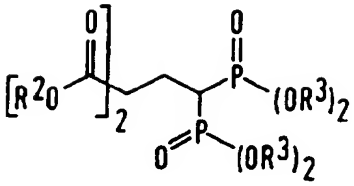


(6)

6. A pharmaceutical composition containing one or more compounds according to any preceding claim and one or more pharmaceutically acceptable carriers, excipients or diluents.

7. A process for the preparation of a compound according to claim 1 which comprises:

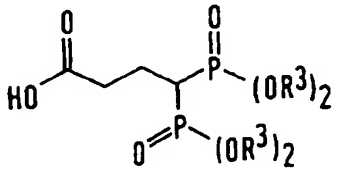
(A) in the preparation of a compound in which X is a group (i), transesterifying the carboxylic ester groups of a compound of formula (7)



(7)

(where R^2 and R^3 are C_{1-6} alkyl groups and may be the same or different) with the hydroxy steroid (StOH), to give a phosphonate ester (8) of the formula $(St\text{-}O\text{-}CO)_2CHCH_2CH(PO(OR_3)_2)_2$, followed by removal of the phosphonate ester groups by hydrolysis;

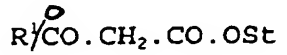
(B) in the preparation of a compound in which X is a group (iii), esterifying the hydroxy steroid (StOH) with the acid (11)



(11)

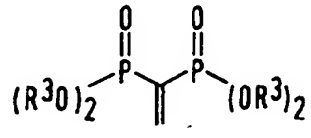
followed by removal of the phosphonate ester groups by hydrolysis; or

(C) in the preparation of a compound in which X is a group (ii), reacting a malonate (13) of the hydroxy steroid

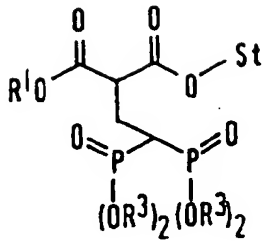


(13)

with a methylidene compound (10)



to give the addition product (14)



(14)

followed by removal of the phosphonate ester groups by hydrolysis.

INTERNATIONAL SEARCH REPORT

[illegible] Application No
PCT/GB 97/01748

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J51/00 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. GUERVENOU ET AL: PHOSPHORUS, SULFUR AND SILICON AND THE RELATED ELEMENTS, vol. 88, no. 1-4, 1995, pages 1-13, XP002040871	1,3,6,7
Y	see the whole document	1-7

X	FR 2 683 527 A (BRETAGNE OCCIDENTALE UNIVERSIT) 14 May 1993	1,3,6,7
Y	see the whole document, in particular example 3, NOTE: formulae of examples 2 and 3 as drawn are incorrect, see text of both examples	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
17 September 1997	03. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Watchorn, P

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INTERNATIONAL SEARCH REPORT

Int[illegible]nal Application No
PCT/GB 97/01748

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 555 845 A (MITSUBISHI CHEM IND) 18 August 1993	1,3,4,6, 7
Y	see page 19, compound 94 and page 35	1-7

Y	EP 0 496 520 A (MERCK & CO INC) 29 July 1992 cited in the application see the whole document	1-7

Y	WO 92 05187 A (BOEHRINGER MANNHEIM GMBH) 2 April 1992 see the whole document	1-7

Y	EP 0 548 884 A (HOECHST JAPAN) 30 June 1993 cited in the application see the whole document	1-7

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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